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A prospective study on antibody response to repeated vaccinations with pneumococcal capsular polysaccharide in splenectomized individuals with special reference to Hodgkin's lymphoma

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Abstract. Landgren O, Björkholm M, Konradsen HB, Söderqvist M, Nilsson B, Gustavsson A, Axdorph U, Kalin M, Grimfors G (Karolinska Hospital and Institutet, Stockholm, Sweden; World Health Organization Collaborating Centre for Reference and Research on Pneumococci, Statens Seruminstitut, Copenhagen, Denmark; Unit of Cancer Epidemiology, Karolinska Hospital and Institutet, Stockholm, Sweden; and University Hospital, Lund, Sweden). A prospective study on antibody response to repeated vaccinations with pneumococcal capsular polysaccharide in splenectomized individuals with special reference to Hodgkin's lymphoma. *J Intern Med* 2004; **255:** 664–673.

Background. Splenectomy is accompanied by a lifelong risk of overwhelming postsplenectomy infection (OPSI), mainly caused by polysaccharide (PS) encapsulated bacteria such as *Streptococcus pneumoniae*. Despite extensive prophylactic efforts the mortality and morbidity rates remain high. The present study was based on a strategy with a predefined vaccination algorithm including repeated 23-valent pneumococcal vaccinations and monitoring of pneumococcal antibody levels. The antibody levels of splenectomized Hodgkin's lymphoma (HL) patients were compared with those patients splenectomized due to immune-mediated cytopenias [autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenic purpura (ITP)] and also individuals who were splenectomized because of trauma (TRAUMA).

Methods. A total of 311 splenectomized individuals were included in this prospective study (208 HL; 15 AIHA; 60 ITP; 28 TRAUMA). Depending on their individual anti-PS antibody levels measured by enzyme-linked immunosorbent assay technique the patients were revaccinated with 23-valent pneumococcal PS vaccine up to four times in accordance with the predefined algorithm. For each vaccination occasion, serum was collected at vaccination, after 1 month ± 2 weeks (peak), and after 1 year ± 6 months (follow-up). Patient files, a national population-based database, and microbiological databases were checked for 124 HL patients to identify OPSI.

Results. A significant response was recorded on primary vaccination as well as on two revaccination occasions for HL, AIHA/ITP, as well as TRAUMA patients. None of the variables age, gender, or time elapsed between splenectomy and first pneumococcal vaccination was found to be associated with mean PS antibody levels at prevaccination, peak or follow-up. No severe adverse events were reported. Amongst 124 clinically monitored HL patients, 10 OPSI were recorded in seven patients during the study period. One of these patients, a middle-aged female, died as a result of fulminant pneumococcal bacteraemia, which was her third OPSI during a 7-year period.

Conclusions. A significant response to pneumococcal PS vaccination was found in all three groups (HL, AIHA/ITP and TRAUMA) of splenectomized patients. Importantly, both primary and repeated vaccinations were safe. Until further knowledge is gained regarding the protective concentration of serotype-specific antibody concentrations we believe that the value of vaccination and frequent revaccination (every 1–5 years) in combination with education of patients and health care professionals and clinical monitoring is beneficial for these patients at risk for OPSI.

Keywords: antibody response, Hodgkin's lymphoma, pneumococcal, revaccination, splenectomy, vaccination.

Introduction

The spleen is an important site of antibody production and phagocytic clearance of blood-borne bacteria, which is facilitated by opsonization with specific antibodies. After splenectomy, relatively higher levels of antibodies are required for maintaining an efficient phagocytosis in the macrophages of the liver [1–3]. Overwhelming postsplenectomy infection (OPSI) was first described in 1952 by King and Schumacker [4], and it is well known that splenectomy is accompanied by a life-long risk of acquiring potentially fatal infections, mainly caused by polysaccharide (PS) encapsulated bacteria, such as *Streptococcus pneumoniae* [5, 6]. According to a recent review, the incidence of postsplenectomy septicaemia and/or meningitis in adults varied from 2.1 to 7.4% over a 30-year period depending on age at splenectomy, cause of splenectomy, and host immunity [7]. Overall, amongst splenectomized individuals the risk of OPSI is especially high in children and in immunodeficient patients. In addition, despite efforts to educate patients and physicians to suspect the diagnosis and initiate adequate treatment promptly if disease occurs the annual mortality rate remains high (1.0–3.8%) [7]. Splenectomized individuals, in particular, patients with Hodgkin's lymphoma (HL) who have received chemotherapy, often show decreased serum immunoglobulin (Ig) levels of the IgM class [8–11]. As previously assumed by Kobel et al., if a young HL patient survives for 50 years after initial treatment, he/she runs a risk of 13.5 and 6.5% to develop and die from OPSI, respectively [12].

The heterogeneity in patient populations and potential protective variation between serotypes may not allow a definition of an effective level of antibodies to prevent OPSI. From the 1970s [13–18] our objective has been to prevent OPSI especially in HL patients by use of education programmes for patients and health care professionals and by providing patients with a 'warning badge' (similar to those carried by cardiac patients treated with pacemakers and/or anticoagulants). Medical records of these patients have been marked with special warning stickers with the same text as the badge. In addition, patients were vaccinated/revaccinated according to a predefined algorithm and were followed clinically [17, 18]. In this study, the pattern of specific IgG antibodies against pneumococcal PS in response to repeated vaccinations with 23-valent PS has been analysed. The overall goal was to improve the management of splenectomized patients. PS antibody levels in splenectomized HL patients were compared with those of previously healthy individuals splenectomized due to trauma and splenectomized patients with immune-mediated cytopenias.

Materials and methods

Patients

Between 1991 and 2002, 311 splenectomized individuals were recruited from 20 hospitals and health care units in Sweden. In total, there were 208 patients with HL, 15 with autoimmune haemolytic anaemia (AIHA), 60 with immune thrombocytopenic purpura (ITP), and 28 individuals who underwent splenectomy due to splenic rupture caused by trauma (TRAUMA). Staging and treatment principles of HL patients have been reported previously [19–22]. The median follow-up time for included patients was 90 months (range 21–144 months). The majority of patients were recruited from Karolinska Hospital ($n = 108$) and Lund University Hospital ($n = 61$). Two hundred and seven (67%) of the included patients had been splenectomized before entry. Many of these had been included in our earlier studies and 177/207 (86%) received their first pneumococcal vaccination (mostly 14-valent pneumococcal vaccine) before inclusion in the current study [14, 15, 17, 18]. The study was approved by the local Ethics Committee. Informed consent was obtained.

Vaccination procedure

All patients were immunized subcutaneously with Pneumovax N® (Merck, Sharp & Dohme, West Point, PA, USA), which contains 25 μg of capsular PS per vaccination dose from each of 23 pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F (according to Danish nomenclature). The patients were revaccinated depending on their individual PS antibody levels as measured by enzyme-linked immunosorbent assay (ELISA) technique (see below) during the study period. Based on the knowledge collected over the past several years from our previous vaccination studies on splenectomized patients, with special reference to HL patients, the following defined algorithm was applied for decision-making regarding revaccination procedures [17, 18]: 1 year after vaccination the PS antibody level was measured. Individuals with a antibody level <0.7 arbitrary units (see below) were revaccinated and in remaining individuals the antibody level was monitored, in most cases annually. If the antibody level was <0.7 at 2 years or <1.5 at 3 or 4 years, revaccination was performed. After 5 years, all individuals were revaccinated, irrespective of PS antibody levels. The distribution of vaccination occasions (per patient) in relation to time to splenectomy and underlying diagnosis is shown in Table 1. For each vaccination occasion, serum was collected at vaccination, 1 month ± 2 weeks after vaccination (peak) and 1 year ± 6 months after vaccination (follow-up). All sera were stored at −70 °C until analysis.

Determination of polysaccharide antibodies

Details of ELISA estimation of PS antibodies have been described previously [17, 18]. In short, 950 μL

Table 1 Patient characteristics, *n* (%)

	HL	AIHA/ITP	Splenectomy due to splenic rupture caused by trauma
No. of patients	208 (100)	75 (100)	28 (100)
Sex			
Male	109 (52)	25 (33)	15 (54)
Female	99 (48)	50 (67)	13 (46)
Age (years) at splenectomy			
<16	9 (5)	3 (4)	2 (7)
16–35	123 (59)	34 (46)	9 (32)
36–55	42 (20)	19 (25)	3 (11)
56–75	5 (2)	12 (16)	2 (7)
>75	0 (0)	1 (1)	0 (0)
No information	29 (14)	6 (8)	12 (43)
First 23-valent pneumococcal polysaccharide vaccination			
Before splenectomy	104 (50)	49 (65)	2 (7)
After splenectomy	66 (32)	20 (27)	25 (89)
No information	38 (18)	6 (8)	1 (4)
No. of vaccinations (per patient)			
1	60 (29)	20 (27)	9 (32)
2	71 (34)	33 (44)	8 (29)
3	57 (27)	20 (27)	8 (29)
>3	20 (10)	2 (2)	3 (10)
[a]Interval (months) between vaccination 2 and 3; median (range)	48 (20–60)[b] 38 (15–60)[c]	42 (15–59)	59 (39–60)

HL, Hodgkin's lymphoma; AIHA, autoimmune haemolytic anaemia; ITP, immune thrombocytopenic purpura. [a]The interval between vaccination 1 and 2 is not given as 86% of the patients received their first pneumococcal vaccination before inclusion in the current study (see also 'Materials and methods'). [b]HL patients who received ≤3 pneumococcal vaccinations. [c]HL patients who received >3 pneumococcal vaccinations (see also Table 2).

diluted patient serum (1 : 1000 phosphate-buffered saline (PBS); PBS with polysorbatum 20; 0.05%; pH 7.4) was absorbed with 50 μL C-PS (diluted to 1 mg mL^{-1} in saline) by incubation for 2 h at 37 °C and additional for 12 h at 4 °C. An equal volume of PBS (pH 7.2) was then added. Pneumococcal C-PS was isolated from a pneumococcal strain with a PS capsule that consists of C-PS (C-mutant CSR, SCS-2, clone 1) by the method of Pedersen et al. [23]. The C-mutant strain was a gift from Markku Koskela, Department of Medical Microbiology, University of Oulu and National Public Health Institute, Oulu, Finland. Polystyrene plates (Microtiter plate M-129B; Dynatech, Chantilly, VA, USA) were coated with the 23-valent pneumococcal PS vaccine as antigen at a concentration of 1 mg L^{-1} for 24 h at 20 °C. After incubation of the serum samples (diluted 1 : 100) overnight, commercially available monoclonal anti-human-IgG antibodies (Seward Laboratories, London, UK) was added. After incubation with rabbit anti-mouse Ig (DAKO Immunoglobulins, Copenhagen, Denmark) alkaline phosphatase-conjugated goat anti-rabbit IgG (Sigma Chemical Company, St Louis, MO, USA) was added and the plates were incubated over night. After washes the plates were incubated with substrate for 10–30 min. Absorbance was measured at 405 nm using a Titertek multiscan (Elflab OY, Helsinki, Finland). In each experiment the absorbance values of a serum pool of 20 healthy normal blood donors, a positive (serum from one individual with high PS antibody level), and a negative (buffer alone) control were included as references.

The serum pool was characterized in relation to the reference serum 89SF USA [24] at the World Health Organization (WHO) Collaborating Centre for Reference and Research on Pneumococci, Statens Seruminstitut, Copenhagen, Denmark. This analysis showed that the serum pool contained the following concentration expressed as mg L^{-1} of the listed serotypes: 1 (4.27), 3 (5.59), 4 (3.20), 7F (2.58), 8 (3.43), 9N (3.87), 14 (8.94), 18C (1.86), 19F (5.89) and 23F (8.24). For each vaccination occasion, antibody fold increase from prevaccination to peak was calculated in relation to dilution curves for the reference serum. Antibody decline was calculated in a similar way from peak to follow-up. As all patients were revaccinated depending on their individual PS antibody levels during the study, all PS antibody ELISA analyses were performed on a consecutive basis. At study closure, serum samples from 10 individuals included at different time periods were selected randomly and re-analysed on a single occasion with the same setting as described above. The correlation between the two measures was very good, $r = 0.95$ (paired sample correlation; $P < 0.001$), but there was a systematic difference between the two with the reanalysis giving values 8.4% (mean) lower than the primary analysis.

All PS antibody analyses were performed at the Hematology Laboratory, Karolinska Hospital.

Determination of type-specific pneumococcal antibodies

Type-specific antibodies against the pneumococcal PS types 1, 4, 7F, 14, 18C, and 19F were measured by use of a micro-ELISA at the WHO Collaborating Centre for Reference and Research on Pneumococci, as described previously [25]. The antibody response to vaccination was described as the geometric means of the absolute antibody concentration, for each of the six serotypes and for the six serotypes combined, and as the geometric mean antibody fold increase. Antibody concentrations were expressed as mg L^{-1} after calibration to the assigned IgG concentrations of the international pneumococcal reference serum 89-SF [24]. The two ELISA methods were compared: serum samples from 10 patients were selected, five with a good and five with a poor response to 23-valent pneumococcal vaccination as estimated with the PS antibody method (see above). The correlation was estimated between the level of log PS antibody fold increase and the log mean level of the serotype specific antibodies fold increase, respectively (Fig. 1; $r = 0.61$ for good responders).

Postsplenectomy infections in Hodgkin's lymphoma patients

Clinical data regarding OPSI were retrieved for all HL patients recruited at Karolinska Hospital and Lund University Hospital ($n = 124$). All available information regarding pneumococcal infections was collected through patient records. In addition, a data file with the unique personal identification numbers (obtained by each Swedish citizen shortly after birth or immigration) of these patients was linked with population-based Swedish Hospital Discharge Register (founded in the 1960s) run by the National

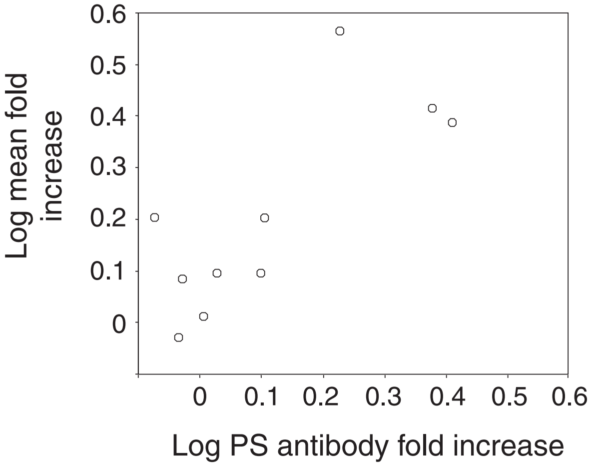

Fig. 1 Correlation between fold increase of polysaccharide (PS) and type-specific pneumococcal antibodies after PS vaccination in splenectomized patients with Hodgkin's lymphoma ($n = 10$).

Board of Health and Welfare, to identify recorded events regarding pneumococcal infections potentially missing in the local files. In addition, the local computer systems (all installed in the late 1980s) at the Departments of Microbiology at Karolinska Hospital, Huddinge University Hospital, and Lund University Hospital were checked to identify registered positive culture results.

Statistical analyses

Differences between means and proportions were tested with Student's t and the chi-square statistics, respectively. Relations between variables were measured with Pearson correlation coefficient and linear regression. For statistical calculations, the antibody concentrations were transformed into logarithms.

Results

Patient characteristics

There were 149 men and 162 women with a median age at splenectomy of 28 years (HL 25, AIHA 25, ITP 33, TRAUMA 26; range 6–81 years). The reported fraction of patients who received their first pneumococcal vaccination before splenectomy within each subgroup was 50% (HL), 65% (AIHA/ITP) and 7% (TRAUMA), respectively (Table 1).

Antibody response to pneumococcal vaccination

Patients with immune mediated cytopenias (AIHA and ITP) did not differ with regard to PS antibody pattern. Data from these individuals were analysed together. The antibody responses of HL patients who were immunized with 23-valent PS vaccine were compared with those of AIHA/ITP, and TRAUMA patients, who were immunized with the same vaccine. The prevaccination, peak and follow-up PS antibody levels were analysed by comparing the mean antibody levels of individuals with complete antibody data (i.e. prevaccination, peak and follow-up antibody data) for each vaccination occasion. A significant response was recorded on all three vaccination occasions for HL, AIHA/ITP and TRAUMA patients, respectively. The same was true when the analysis was restricted to individuals with complete information (Fig. 2).

Factors associated with prevaccination, peak and follow-up antibody levels

None of the variables age, gender, or time elapsed between splenectomy and first pneumococcal vaccination were significantly associated with the mean PS antibody levels at prevaccination, peak or follow-up when tested univariately for each vaccination occasion. However, HL patients who received ≤ 3 vaccinations had higher mean peak and follow-up antibody levels than those who were revaccinated on >3 occasions (Table 2).

Pneumococcal infections in patients with Hodgkin's lymphoma

Amongst HL patients recruited from Karolinska Hospital and Lund University Hospital ($n = 124$), 10 OPSI were recorded in seven patients as described below (Table 3): in two patients (no. 1 and 2), naso-pharyngeal colonization by pneumococci in association with pneumonia was found. Patient no. 3 was diagnosed with pneumococcal meningitis. In four patients (no. 4, 5, 6 and 7) pneumococcal bacteraemia was diagnosed. In patient no. 6, type determination showed occurrence of pneumococcal serogroup 6. In this patient the antibody levels declined to prevaccination levels shortly after given vaccinations (approxi-

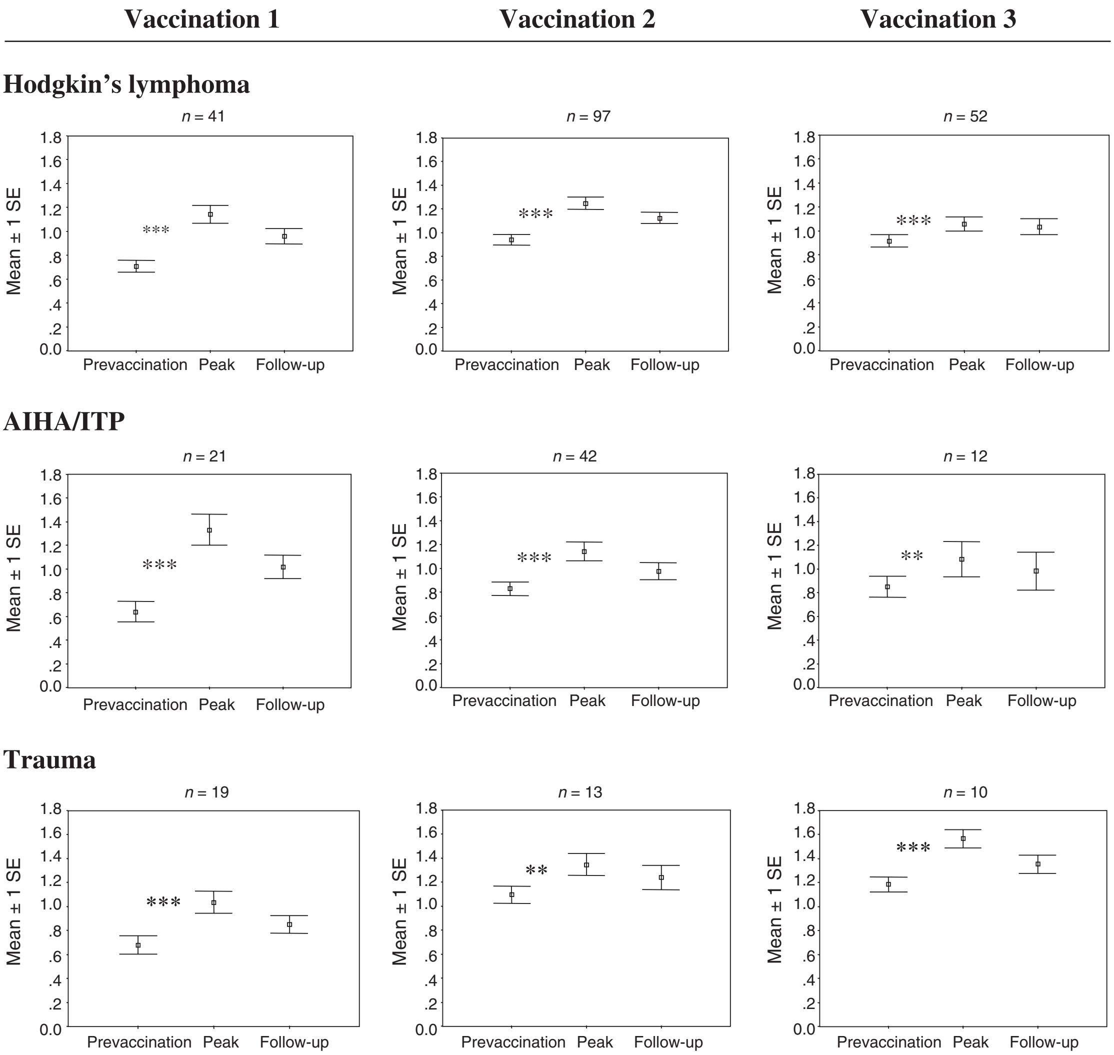

Fig. 2 Antibody levels at peak and follow-up after repeated pneumococcal vaccination (arbitrary units; mean ± 1 SE). SE, standard error; prevaccination = before given pneumococcal vaccination; peak = 1 month ± 2 weeks after given pneumococcal vaccination; follow-up = 1 year ± 6 months after given pneumococcal vaccination; AIHA, autoimmune haemolytic anaemia; ITP, immune thrombocytopenic purpura; TRAUMA, splenectomy due to splenic rupture caused by trauma; **significant ($P < 0.01$) and ***($P < 0.001$) response to the vaccination; antibody response as estimated with the 23-valent pneumococcal polysaccharide vaccine as antigen; analysis restricted to include data from individuals with complete information (i.e. prevaccination, peak and follow-up PS antibody levels).

mately 1–2 years later; data not shown). As a consequence, he was recommended revaccination every second year. OPSI was successfully treated in all these patients. However, 49 months after her first pneumococcal infection, patient no. 7 had a second episode of severe pneumococcal bacteraemia with a prompt response to treatment. Unfortunately, two and a half years later she died from a fulminant pneumococcal (serotype 38) bacteraemia. Antibody levels following revaccination were not available in this patient.

Discussion

Fulminant, potentially life-threatening infection mainly due to *Streptococcus pneumoniae* is a major well known risk after splenectomy [5, 6]. Strategies to prevent OPSI include immunization, antibiotic prophylaxis and education. In the present study, we chose a strategy based on a predefined vaccination algorithm using a 23-valent pneumococcal vaccine and longitudinal monitoring of PS antibodies. The algorithm was based on our previous experience

Table 2 Peak and follow-up antibody levels (arbitrary units; mean; 95% confidence interval) in patients with Hodgkin's lymphoma according to number of vaccinations

Vaccination occasion	Patients given ≤3 pneumococcal vaccinations	Patients given >3 pneumococcal vaccinations	*P*-value
Peak			
First vaccination	1.18 (1.03–1.34)	1.04 (0.76–1.30)	0.398
Second vaccination	1.26 (1.15–1.37)	1.05 (0.85–1.26)	0.176
Third vaccination	1.21 (1.08–1.34)	0.94 (0.71–1.18)	0.051
Follow-up			
First vaccination	1.04 (0.90–1.19)	0.81 (0.57–1.06)	0.235
Second vaccination	1.18 (1.09–1.28)	0.92 (0.73–1.10)	0.059
Third vaccination	1.17 (1.01–1.34)	0.84 (0.64–1.04)	0.024

Antibody response as estimated with the 23-valent pneumococcal polysaccharide vaccine as antigen.

Table 3 Reported overwhelming postsplenectomy infection (OPSI) amongst splenectomized Hodgkin's lymphoma patients ($n = 124$)

Patient no.	Age (years) at first OPSI	Sex	OPSI in relation to given vaccinations	Response to vaccination
1	40	Female	Pneumonia with naso-pharyngeal colonization by pneumococci	
			First vaccination 66 months before event	No information
			Second vaccination 77 months after event	Good
			Third vaccination 124 months after event	Good
2	33	Female	Pneumonia with naso-pharyngeal colonization by pneumococci	
			First vaccination in relation to event	Good
3	37	Female	Pneumococcal meningitis	
			First vaccination 32 months after event	No information
			Second vaccination 182 months after event	Good
			Third vaccination 221 months after event	Good
			Fourth vaccination 264 months after event	Good
4	42	Female	Pneumonia with positive blood culture for pneumococci	
			First vaccination in relation to event	Good
5	27	Male	Pneumococcal bacteraemia	
			First vaccination 198 months after event	Good
6	61	Male	Pneumococcal bacteraemia; type determination showed serogroup 6	
			First vaccination 179 months before event	No information
			Second vaccination 29 months before event	No information
			Third vaccination 6 months after event	Good
			Fourth vaccination 22 months after event	Good
			Fifth vaccination 40 months after event	Poor
			Sixth vaccination 45 months after event	Poor
7	48	Female	Pneumococcal bacteraemia	
			First vaccination 10 months before event	Poor
			Second vaccination 38 months after event	No information
			Pneumococcal bacteraemia 49 months after first event	
			Fatal pneumococcal bacteraemia 81 months after first event; type determination showed serotype 38	

with pneumococcal vaccination/revaccination in these patient categories [17, 18]. The antibody levels of splenectomized HL patients were compared with those patients splenectomized due to immune mediated cytopenias (AIHA/ITP) and also individuals who were splenectomized because of TRAUMA. A significant antibody response to primary immunization with pneumococcal PS vaccine was observed in all three groups. These findings are in accordance with previous studies [17, 26, 27] showing pneumococcal antibody response in splenectomized HL to be normal or almost normal if the vaccination was not undertaken during active cytoreductive treatment and/or radiotherapy as discussed below.

Response to pneumococcal revaccination has been studied primarily in elderly previously healthy individuals and certain selected risk groups such as renal transplant recipients and haemodialysis patients [28–32]. In these studies, a better antibody response to primary vaccination in comparison with revaccination has been reported, in accordance with the findings of the present study. However, a significant response was noted in all three subgroups, also to the second revaccination. The algorithm for revaccination based on antibody level monitoring contributed to a selection of patients with less marked responses amongst patients receiving >3 vaccinations. Thus, approximately 20% of HL patients had a poor antibody response following both primary and later vaccinations. Overall, antibody levels decline in many individuals, most conspicuously in patients with an underlying immunodeficiency. It seems logical to have a liberal attitude to revaccination in these patients. Importantly, none of our patients experienced any severe adverse reaction as a result of repeated vaccinations.

It is generally agreed that B-lymphocyte functions are well preserved in untreated HL patients, except in patients with generalized disease [33–35]. A normal response to immunization with pneumococcal PS vaccine is reported in untreated HL patients [26, 27]. However, an impaired response to vaccination is frequently recorded shortly following termination of treatment [36–39]. Eventually, HL patients regain their capacity to respond to PS vaccination [40, 41]. Increased age is also reported to be a factor associated with a poor response to immunization [40, 42]. However, in the present study we found no association between age at splenectomy, gender, or time elapsed between splenectomy and first pneumococcal vaccination and the PS antibody levels at prevaccination, peak, or follow-up.

Ten OPSI in seven patients were recorded amongst the 124 HL patients during the 11-year study period. Thus, the annual incidence of OPSI was approximately 0.5% which is lower than that recorded in most previous reports (for review see Ref. [7]). These results therefore indicate that revaccination in combination with education and clinical monitoring may contribute to a reduction of OPSI in HL patients. Similar results were achieved in a Danish study again based on a defined programme of pneumococcal vaccination and prophylactic antibiotics in splenectomized children [43]. Our patient (no. 7), who suffered three OPSI during a 7-year period and unfortunately died during the third episode, clearly illustrates the persisting risk of fatal infections in splenectomized individuals. In the present series only one patient with OPSI was above the age of 50, in good accordance with a recent study where almost two-thirds of the fatalities occurred in individuals under 50 years of age [44]. Importantly, four of seven (57%) patients developed OPSI before pneumococcal vaccination, in line with the fact that <60% of persons for whom pneumococcal vaccination is recommended have been vaccinated [45–47].

We are well aware of the limitations of the currently used ELISA method. For example, the method is based on an arbitrary scale and absolute quantification of antibody concentrations in serum in mg L^{-1} cannot be accomplished. In addition, the method does not include serotype analyses. However, this study was planned and initiated more than 10 years ago, i.e. patients have been monitored according to the same protocol by the same technician in the same laboratory during the whole study period. We have experience from this method in other studies [17, 18] and we have continuously validated the reproducibility of results obtained. In the present study, we have correlated our estimated arbitrary PS antibody levels to those of serotype-specific antibodies as determined by an internationally accepted reference method [25], clearly indicating that the precision has been acceptable for the purpose to estimate response to 23-valent PS vaccination (Fig. 1).

Due to the introduction of combined modality treatment including brief chemotherapy for patients with limited stage HL and new noninvasive staging techniques HL patients today only rarely undergo exploratory laparotomy with splenectomy [for review see Ref. [48]). However, previously splenectomized HL patients carry a life-long increased risk of OPSI. In addition, still patients with lymphoma and other haematological disorders undergo splenectomy [48] and in some patients splenic preservation may not be feasible following splenic trauma [49]. For these patient categories it is reassuring that preventive measures are accessible.

In conclusion, OPSI in splenectomized patients still poses a clinical challenge and fatalities are still observed despite active preventive measures. In this study, a significant response to pneumococcal vaccination was found in splenectomized HL, AIHA/ITP and TRAUMA patients. Importantly, both primary and repeated vaccinations were safe. Until further knowledge is gained regarding the protective concentration of serotype-specific antibody concentrations we believe vaccination as well as frequent revaccination (every 1–5 years) in combination with education of patients and health care professionals and clinical monitoring to be the most beneficial management of patients at risk for OPSI. Thus, we support the recommendations from the Centers for Disease Control and Prevention (CDC) [50] (revaccination every 6 years) and the British Committee for Standards in Haematology [51] (revaccination every 5–10 years or sooner), however, emphasizing the rather frequent need for shorter intervals between revaccinations to keep antibody concentrations at a level with a high probability to confer protection. Our results suggest that this is possible to accomplish without significant side-effects. Immunization with pneumococcal conjugate vaccines will probably be part of an optimized management programme for these patients in the future and such studies are ongoing.

Conflict of interest statement

No conflict of interest was declared.

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